1. Claims 1-12, 13-15 and 17-21 were rejected under U.S.C. §112, first paragraph. Claim 1, as amended now recites a recombinant attenuated *Salmonella* cell. A Declaration under 37 C.F.R. 1.132 is being concurrently filed with this Amendment. The Declaration illustrates a prophylactive live vaccine approach to protect against *H. pylori* infection in mice. Specific protection to the recombinant *H. pylori* antigens expressed by a live vector is achieved. Applicants' respectfully submit that amended claim 1 and the Declaration overcome the rejection and request that claims 1-12, 13-15, and 17-21 be allowed.

2. Claims 1, 2, 5 and 10 were rejected under U.S.C. § 102(b) as being anticipated by Evans et al. The Office Action notes that Evans used *E. coli*, an entero-bacterial cell for the production of an attenuated microbial pathogen. Evans does not teach *Salmonella* for the production of an attenuated microbial pathogen. Applicants' claims are limited to *Salmonella*, and Applicants' previous arguments are commensurate with the scope of these claims.

Since Evans fails to recite all the elements of the presently claimed invention, Evans is an improper basis for rejection under U.S.C. § 102(b) and Applicants' respectfully request that this rejection be withdrawn.

3. Claims 1, 2 and 5-10 were rejected under U.S.C. § 102(b) as anticipated by Odenbreit et al (April 1996).

Odenbreit discloses recombinant *E. coli* cells expressing portions of *Helicobacter* antigens. Claim 1, as twice amended, now expressly limits the recombinant attenuated microbial pathogen to *Salmonella*. Claims 2 and 5-10 still depend from claim 1.

Since Odenbreit fails to recite all of the elements of the presently claimed invention, it is an improper basis for rejection under U.S.C. § 102(b). Therefore, Applicants' respectfully request that this rejection be withdrawn.

4. Claims 1, 2, 5, 10, 11, 13 and 17-21 were rejected under U.S.C. § 102(b) as anticipated by Doidge in light of McGhee. Applicants respectfully submit that neither reference anticipates or suggests Applicants' presently claimed invention.

Doidge and McGhee disclose a vaccine which acts protectively against *H. felis*. Doidge and McGhee fail to show protection against *H. pylori*.

Further, McGhee et al. comments that "antigens delivered by live vectors such as *Salmonella typhimurium* in the murine system and *Salmonella typhi* in humans must consider T-cell responses induced against a live vector in addition to the inserted recombinant antigen" and furthermore, "one must consider an appropriate balance between Th1 and Th2 cells for the induction of antigen-specific IgA responses." Each microbial infection induced by a pathogen needs a specific type of balanced immune response. The response cannot be foreseen, but must be evaluated individually. McGhee et al. provides no indication as to how such an appropriate balance could be obtained. Therefore, at the time the present invention was filed, McGhee et al. was unable to indicate whether oral immunization with a heterologous *Salmonella* live vaccine would be suitable for the prevention or treatment of *Helicobacter* infections. Although Doidge et al. proposes that a recombinant *Helicobacter* live vaccine might be used for the treatment of *Helicobacter* infections, no such evidence was presented. These references offer mere speculation and lack any suggestion of a likelihood of

success. Applicants note that lacking any guidance as to how to proceed, those of skill in the art would not know how to make or use the present invention.

5. Claims 1, 2, 4, 5, 10 and 17 were rejected under U.S.C. § 102(b) as being anticipated by Dore'-Davin et al. (May 1996).

Dore'-Davin et al. discloses *E. coli* expression vectors containing DNA sequences encoding the urease B subunit of *H. pylori* for protection against *H. felis*. In Dore-Davin et al., recombinant *E. coli* bacteria expressing fragments of the urease B of *Helicobacter* were used as a source for the production and isolation of these peptides, which were then administered as an oral vaccine with the cholera toxin adjuvant.

Dore'-Davin et al. fails to teach *Salmonella* for the production of an attenuated microbial pathogen. Now Applicants' claims are directed to *Salmonella,* and Applicants' previous arguments are commensurate with the scope of these claims.

Since Dore'-Davin fails to recite all of the elements of the presently claimed invention, it is an improper basis for rejection under U.S.C. § 102(b). Therefore, Applicants' respectfully request that this rejection be withdrawn.

6. Claims 1, 2, 4, 5, 10, 11, 12-35 and 17-21 were rejected under U.S.C. § 102(b) as being anticipated by Michetti (WO95/22987).

Michetti et al. discloses the administration of a composition comprising *Helicobacter* urease peptides wherein such composition comprises a recombinant live vector which expresses a *Helicobacter* urease peptide. However, Michetti et al. discloses only the use of purified, enzymatically inactive urease with cholera toxin as an adjuvant as a formulation for oral immunization.

Since Michetti fails to recite all of the elements of the presently claimed invention, it is an improper basis for rejection under U.S.C. § 102(b). Therefore, Applicants' respectfully request that this rejection be withdrawn.

7. Claims 1-11, 13-15 and 17-21 were rejected under U.S.C. § 103(a) as being unpatentable over Michetti in view of Russell et al.

In addition to the discussion of Michetti above, it should also be noted that Michetti does not show a protective immune response induced by a live carrier vaccine based on, for example, *Salmonella* (Table I of Michetti shows protection after immunization with purified urease). Michetti suggests that urease might be expressed by a live carrier, but fails to teach how. Natural infection with *H. pylori* leads to a non-protective immune response, which because of the *Helicobacter*-specific antibody subclasses formed and the pro-inflammatory cytokines measurably formed, is classified as Type I. Michetti et al. uses an immunization protocol (CTXB + urease), which is known to induce both a humoral and cellular immune response of Type II. The protection against *H. felis* is also shown. *Salmonella*, however, produce an immune response of Type I. Hence, the results of Michetti do not suggest that *Salmonella* might be capable of producing a live vaccine.

Russell provides no teaching or suggestion for a protective oral live vaccine consisting of an attenuated bacterial carrier that expresses a *Helicobacter* immunogen on its own (non-chimeric), as is claimed in the present invention. In the present invention, surprisingly, an attenuated bacterial carrier expressing a *Helicobacter* immunogen shows remarkable efficacy. A single dose is sufficient to induce protective immunity of about 100% without use of additional adjuvants. The disclosure of Russell

et al. merely provides information regarding humoral responses, and thus contains no disclosure as to whether a CT A2/B chimeric protein expressed in an attenuated bacterial carrier would indeed induce such a high level of protective immunity after a single oral application. Here, single dose is emphasized to illustrate remarkable efficacy, as opposed to treatment limitations. Moreover, Russell et al. uses cholera toxin A2/B, which stimulates a humoral immune response, as an adjuvant.

For the foregoing reason there is no disclosure in Michetti or Russell which would suggest Applicants' presently claimed invention. Similarly, there is no disclosure or teaching in either of those references which would suggest the desirability of combining any portions thereof effectively to anticipate or suggest Applicants' presently claimed invention. Accordingly, reconsideration and withdrawal of these grounds of rejection are respectfully requested.

8. Claims 1-4 and 7-11 were rejected under U.S.C. § 103(a) as being unpatentable over Russell et al. (U.S. Pat. No. 6,030,624) in view of Bukanov et al (1994).

Russell et al. discloses a method of producing an immune response by oral administration of an attenuated strain of bacteria (e.g. aroA and aroD mutant *Salmonella typhimurium*) wherein said attenuated bacteria expresses an antigen of interest as a cholera toxin A2/B chimeric protein.

Bukanov et al. provide a genetic analysis of a variety of *Helicobacter* genes including virulence factors such as vacA, cagA, ureAB, ureD and ureH.

The cited references Russell et al. and Bukanov et al. provide no suggestion or motivation regarding the *Helicobacter* immunogen or live vaccine of the present

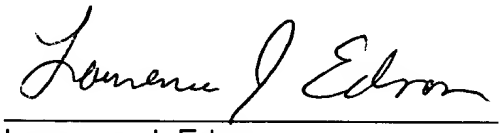
invention. Russell et al. teaches the expression of cholera toxin A2/B as a fusion protein which has immunogenic properties to induce a humoral response. However, Russell et al. does not teach or suggest an attenuated pathogen comprising a *Helicobacter* immunogen which is capable of inducing protective immunity. Nor does Russell et al. teach or suggest *Helicobacter* immunogens which are expressed in an attenuated bacterial carrier without cholera toxin A2/B as a fusion partner as in the present invention. As noted above, such formulations are capable of inducing protective immunity of about 100% after a single dose application. Applicants note that Bukanov et al. fails to cure any of the deficiencies of Russell et al.

For the foregoing reasons, Applicants' claims now particularly point out and distinctly claim what Applicants regard as their invention in a manner patentably distinguished over all grounds of rejection cited in the Office Action. Accordingly, allowance of all claims 1-11, 13-15 and 17-21 is respectfully requested.

Should the Examiner deem that any further action by the Applicants would be desirable for placing this application in even better condition for issue, the Examiner is requested to telephone applicants' undersigned representative at the number listed below.

Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300.

Respectfully submitted,



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Attachment: Declaration under 37 C.F.R. 1.132

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MARKED-UP VERSION OF ORIGINAL CLAIMS

1. **(Twice Amended)** A recombinant attenuated [microbial]*Salmonella* [pathogen]cell, which comprises at least one heterologous nucleic acid molecule encoding a *Helicobacter* immunogen, wherein said attenuated pathogen is capable of expressing said nucleic acid molecule or capable of causing the expression of said nucleic acid molecule in a transformed target cell, and wherein said immunogen is capable of inducing protective immunity.

22. **(New)** A method of inducing protective immunity against a *Helicobacter* infection in a mammalian host comprising: administering to a mammalian host in need of protective immunity an effective amount of the cell of claim 1.